# WO9616016

Publication Title:

NOVEL (+)-(S)-2-(3-BENZOYLPHENYL)PROPIONIC ACID DERIVATIVES WITH ANALGESIC ACTION AND THE PROCESS FOR THE PREPARATION THEREOF

Abstract:

Abstract of WO 9616016

(A1) Translate this text The present invention relates to novel (+)-(S)-2-(3-benzoylphenyl)propionic acid salts of formula (I), wherein B<+> is choline or the protonated form of lysine, arginine, ornithine, D-glucamine, N-methyl-D-glucamine or imidazole. The process for the preparation comprises reacting a compound of formula (II) with lysine, arginine, ornithine, choline hydroxide, D-glucamine, N-methyl-D-glucamine or imidazole; or reacting a salt of the compound of formula (II) with the suitable organic salt. Said compounds have a high analgesic and antiinflammatory activity.

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

**(51) International Patent Classification** 6 :
**C07C 59/84, A61K 31/19**

**A1**

**(11) International Publication Number:** **WO 96/16016**

**(43) International Publication Date:** 30 May 1996 (30.05.96)

**(21) International Application Number:** PCT/EP95/04554

**(22) International Filing Date:** 20 November 1995 (20.11.95)

**(30) Priority Data:**
P 9402406 23 November 1994 (23.11.94) ES

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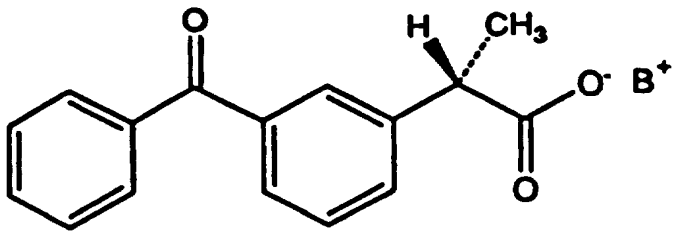
**(81) Designated States:** AL, AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MX, NO, NZ, PL, PT, RO, RU, SE, SG, SI, SK, TJ, TM, TT, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, LS, MW, SD, SZ, UG).

**Published**
*With international search report.*
*Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.*

**(54) Title:** NOVEL (+)-(S)-2-(3-BENZOYLPHENYL)PROPIONIC ACID DERIVATIVES WITH ANALGESIC ACTION AND THE PROCESS FOR THE PREPARATION THEREOF

**(57) Abstract**

The present invention relates to novel (+)-(S)-2-(3-benzoylphenyl)propionic acid salts of formula (I), wherein $B^+$ is choline or the protonated form of lysine, arginine, ornithine, D-glucamine, N-methyl-D-glucamine or imidazole. The process for the preparation comprises reacting a compound of formula (II) with lysine, arginine, ornithine, choline hydroxide, D-glucamine, N-methyl-D-glucamine or imidazole; or reacting a salt of the compound of formula (II) with the suitable organic salt. Said compounds have a high analgesic and antiinflammatory activity.

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# NOVEL (+)-(S)-2-(3-BENZOYLPHENYL)PROPIONIC ACID DERIVATIVES WITH ANALGESIC ACTION AND THE PROCESS FOR THE PREPARATION THEREOF

The present invention relates to novel (+)-(S)-2-(3-benzoylphenyl)propionic acid derivatives, namely the salts with basic amino acids, amines or basic heterocycles, the pharmaceutically acceptable solvates thereof, and the pharmaceutical compositions containing them, having anti-inflammatory and analgesic activities. The present invention also relates to a process for the preparation of the novel salts and the therapeutical use thereof.

## TECHNOLOGICAL BACKGROUND

2-(3-Benzoylphenyl)propionic acid, also named ketoprofen, is a known non-steroidal anti-inflammatory agent exhibiting a potent analgesic and antipyretic action.

Though ketoprofen has been marketed as a racemic mixture of its (+)-(S) and (-)-(R) enantiomers, its therapeutical activity has been found to lie mainly in the S enantiomer [Yamaguchi T. et al., *Folia Pharmacol. Japon* 90, 295 (1987)]. Moreover, the (+)-(S) enantiomer of ketoprofen has been claimed to be a faster acting and more potent analgesic than the racemate, when administered at equal doses [Sunshine A. et al., WO 89/04658].

Structurally ketoprofen, similarly to other arylpropionic acids, has a lipophilic aromatic moiety which is responsible for its poor solubility in water and a free carboxylic group which has been related to

its ulcerogenic toxicity. These drawbacks can restrict its use, since its poor solubility makes both the parenteral and oral administrations difficult, and its tendency to cause gastric lesions limits its use in patients prone to gastrointestinal disorders.

According to literature, said drawbacks of arylpropionic acids may substantially be overcome by salifying them with metals, to give salts such as ketoprofen sodium, zinc or aluminium salt [Fujimura H. et al., *Oyo Yakuri*, 13, 709 (1977), Buxadè A. ES 2016503, Montanari R. DE 3505582, respectively]; with basic amino acids such as ibuprofen [Kwan K.Ch. EP 424028] and ketoprofen [Metz G. EP 136470, BE 882889, Bruzzese T. et al., DE 2508895] lysine salts; amine salts such as diclofenac choline salt [Di Schiena M.G. EP 521393]; salts with basic heterocycles such as ketoprofen imidazolium salt [Stradi R. FR 2580641].

(+)-(S)-2-(3-Benzoylphenyl)propionic acid tromethamine salt has also been described [Carganico G. et al., WO 94/11332]; undoubtedly, up to now, no salts of the present invention have been described in literature, therefore said compounds can be considered an alternative to the above cited tromethamine salt.

Nevertheless, in therapy there is a need for compounds with high anti-inflammatory and analgesic activities, free from undesired side-effects. The present invention provides a series of novel compounds showing the cited anti-inflammatory and analgesic actions, together with a very reduced gastrolesivity.

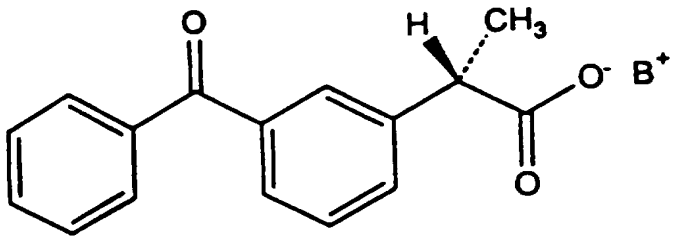
The novel salts have a high solubility in water which allows for them to be administered both

intramuscularly and intravenously, as well as orally in the form of tablets which are easy to dissolve in a very short time. These novel derivatives exhibit a fast, complete adsorption both in animals and humans, showing an action and analgesic response higher than those of the corresponding racemic ketoprofen salts.

Moreover, said characteristics of the compounds of the present invention allow to attain the same analgesic therapeutical effectiveness using doses lower than those necessary for racemic ketoprofen, either free or salified. Further, the physico-chemical and pharmacokinetic properties of the compounds of the present invention give them a therapeutical advantage compared with the use of the (+)-(S) enantiomer of ketoprofen in the free acid form, claimed in the above cited patent [Sunshine A. et al., WO 89/04658], also showing an additional advantage, since they can be administered to patients prone to gastrointestinal disorders when treated with ketoprofen free acid and can be considered an alternative to the metal salts when the metal retention is contra-indicated, for example in case of patients suffering from cardiac disorders or hypertension.

**DISCLOSURE OF THE INVENTION**

The present invention provides novel salts of general formula (I),



I

wherein:

$B^+$ is choline or the protonated form of lysine, arginine, ornithine, D-glucamine, N-methyl-D-glucamine or imidazole.

The present invention also provides a process for the preparation of the novel (+)-(S)-2-(3-benzoyl-phenyl)propionic acid salts, as well as the therapeutical use thereof.

Object of the present invention are also the solvates of the compounds of formula (I).

The present invention also includes all the possible stereoisomers of the compounds of formula (I) as well the mixtures thereof.

Preferred compounds of the present invention are those wherein $B^+$ is choline or the protonated form of L-lysine, DL-lysine, L-arginine, DL-arginine, N-methyl-D-glucamine or imidazole.

Particularly preferred compounds of the present invention are the following ones:

(+)-(S)-2-(3-benzoylphenyl)propionic acid L-lysine salt;

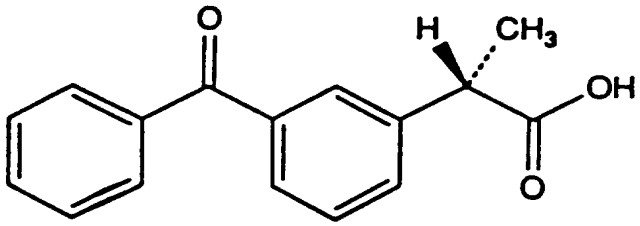
(+)-(S)-2-(3-benzoylphenyl)propionic acid DL-lysine salt;

(+)-(S)-2-(3-benzoylphenyl)propionic acid choline salt;

(+)-(S)-2-(3-benzoylphenyl)propionic acid N-methyl-D-

glucamine salt;
(+)-(S)-2-(3-benzoylphenyl)propionic acid imidazole salt.

According to the present invention, the compounds of formula (I) are obtained by reacting (+)-(S)-2-(3-benzoylphenyl)propionic acid (II)




II

with lysine, arginine, ornithine, choline hydroxide, D-glucamine, N-methyl-D-glucamine or imidazole; or by reacting a (+)-(S)-2-(3-benzoylphenyl)propionic acid (II) salt, prepared in situ (preferably the sodium salt) with the suitable organic salt, such as lysine, arginine or ornithine hydrochloride or choline chloride. The reaction is carried out preferably in equimolar amounts, in a solvent or in a mixture of polar solvents such as water, ethanol, isopropanol, methanol, tetrahydrofuran or acetone. Preferably, a mixture of water with methanol or ethanol is used and, when employing the sodium salt of the compound of formula (II), ethanol or isopropanol with a low water content are preferably used to promote the precipitation of sodium chloride formed during the reaction. The reaction temperature can vary between 0°C and the solvent reflux, for a time between 1 and 24 hours.

The starting (+)-(S)-2-(3-benzoylphenyl)propionic acid (II) can be prepared following the procedures

described in literature, for example by enantioselective synthesis [Fadel A., *Synlett.* 1, 48 (1992)], or by resolution of racemic ketoprofen through crystallization with chiral amines or enzymatic methods [Nohira H. et al., EP 423467, Sih C.L. et al., EP 227078, Carganico G. et al., WO 93/25703, WO 93/25704, Evans C. et al., WO 93/04189, WO 93/04190, Warneck J. et al., WO 94/20633].

The compounds of the present invention have anti-inflammatory and analgesic characteristics and therefore they can be used in human therapy.

For the therapeutical use, the compounds of the present invention are formulated in suitable pharmaceutical forms, according to conventional techniques and excipients, such as those described in Remington's Phramaceutical Handbook, Mack Pub. Co., N.Y., USA. Examples of such formulations include capsules, tablets, granulates, solutions, syrups and the like, containing 1 to 1000 mg per unitary dose.

The following examples illustrate the preparation and the results of the pharmacological activity tests of the compounds of the present invention, without limiting it.

EXAMPLE 1

Preparation of (+)-(S)-2-(3-benzoylphenyl)propionic acid L-lysine salt

To a solution of (+)-(S)-2-(3-benzoyl-phenyl)propionic acid (5.0 g, 19.7 mmol) in ethanol (8 ml), a solution of L-(+)-(S)-lysine (2.85 g, 19.5 mmol) in water (10 ml) was added. The mixture was stirred at room temperature for 1 hour, thereafter was evaporated to dryness to obtain a semi-solid residue which was

redissolved in ethanol and evaporated to dryness to obtain a solid, which was digested in ethyl ether (3x50ml), filtered and dried under vacuum. 6.59 g (84%) of the title compound were obtained as a white solid with melting point 141.8-142.6°C.

$[\alpha]_D^{25}$ = +3.07° (c = 1.24, water).

IR (KBr): 2960, 2930, 1650, 1640, 1600, 1570, 1490, 1400, 1360, 1290, 720, 650 $cm^{-1}$.

1H N.M.R. (300 MHz, $CD_3OD$) δ ppm: 1.45 (d, 3H); 1.48 (m, 2H); 1.64 (m, 2H); 1.84 (m, 2H); 2.88 (t, 2H); 3.55 (t, 1H); 3.66 (q, 1H); 7.41-7.80 (m, 9H).

Elemental analysis: calculated for $C_{22}H_{28}N_2O_5$: C, 65.98%; H, 7.05%; N, 6.99%. Found: C, 65.79%; H, 7.14%; N, 6.99%.

EXAMPLE 2

Preparation of (+)-(S)-2-(3-benzoylphenyl)propionic acid DL-lysine salt

(+)-(S)-2-(3-Benzoylphenyl)propionic acid was reacted with DL-lysine analogously to what described in Example 1. A water-soluble white solid was obtained.

EXAMPLE 3

Preparation of (+)-(S)-2-(3-benzoylphenyl)propionic acid choline salt

To a choline hydroxide aqueous solution (0.95 g, 7.87 mmol), (+)-(S)-2-(3-benzoylphenyl)propionic acid (2.0 g, 7.87 mmol) was added. The mixture was heated to 60°C for 10 hours, thereafter was evaporated to dryness, to obtain a semi-solid residue which was redissolved in ethanol and evaporated to dryness. The resulting solid was filtered and washed with ethyl ether. 2.52 g (89%) of a white solid were obtained.

Elemental analysis: calculated for $C_{21}H_{27}NO$: C, 70.56%; H, 7.61%; N, 3.92%. Found: C, 70.12%; H, 7.31%; N, 3.62%.

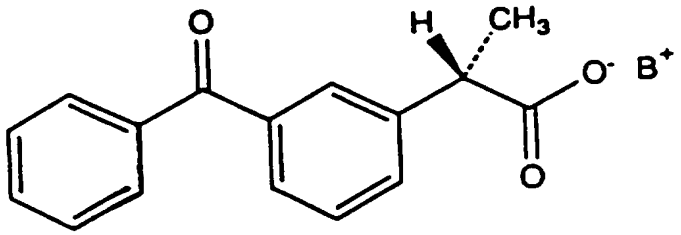
EXAMPLE 4

Preparation of (+)-(S)-2-(3-benzoylphenyl)propionic acid N-methyl-D-glucamine salt

To a solution of (+)-(S)-2-(3-benzoylphenyl)propionic acid (2.5 g, 9.8 mmol) in ethanol (10 ml), a solution of N-methyl-D-glucamine (1.01 g, 9.8 mmol) in water (12 ml) was added. The mixture was stirred at 30°C for 1 hour, thereafter was evaporated to dryness. The resulting residue was redissolved in ethanol and evaporated to dryness. The obtained solid was digested with cold ethyl ether, filtered and dried under vacuum. 3.97 g (90%) of a white solid were obtained.

CLAIMS

1. A compound of formula (I),



I

wherein:

$B^+$ is choline or the protonated form of lysine, arginine, ornithine, D-glucamine, N-methyl-D-glucamine or imidazole; all the possible stereoisomers of compound (I) and the mixtures thereof, as well as the pharmaceutically acceptable solvates of compound (I).

2. A compound according to claim 1, wherein $B^+$ is choline or the protonated form of L-lysine, DL-lysine, L-arginine, DL-arginine, N-methyl-D-glucamine or imidazole.

3. A compound according to the above claims, selected from:

(+)-(S)-2-(3-benzoylphenyl)propionic acid L-lysine salt;

(+)-(S)-2-(3-benzoylphenyl)propionic acid DL-lysine salt;

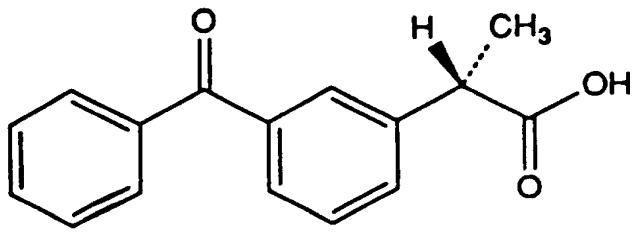
(+)-(S)-2-(3-benzoylphenyl)propionic acid choline salt;

(+)-(S)-2-(3-benzoylphenyl)propionic acid N-methyl-D-glucamine salt;

(+)-(S)-2-(3-benzoylphenyl)propionic acid imidazole salt.

4. A process for the preparation of the compounds of

general formula (I) of claim 1, which process comprises reacting a compound of formula (II):




II

with lysine, arginine, ornithine, choline hydroxide, D-glucamine, N-methyl-D-glucamine or imidazole; or reacting a salt of the compound of formula (II), prepared in situ, with the suitable organic salt selected from lysine, arginine or ornithine hydrochloride or choline chloride, the reaction being carried out in a solvent or in a mixture of polar solvents, selected from water, ethanol, isopropanol, methanol, tetrahydrofuran or acetone.

5. A process according to claim 4, wherein the salt of compound (II) prepared in situ is the sodium salt.

6. A process according to claim 4, wherein the solvent is a mixture of water and methanol or ethanol, and, when using the sodium salt of the compound of formula (II), low water content ethanol or isopropanol are used.

7. The use of a compound according to any one of claims 1 to 3 for the preparation of a medicament for producing a rapid, high analgesic response in humans.

8. The use of a compound according to any one of claims 1 to 3 for the preparation of a medicament for the treatment of pain and inflammation in humans.

9. Pharmaceutical compositions containing a therapeutically effective amount of a compound according to claims 1 to 3, together with a pharmaceutically acceptable excipient.

# INTERNATIONAL SEARCH REPORT

Int ional Application No
PCT/EP 95/04554

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07C59/84 A61K31/19

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07C A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | WO,A,94 20449 (DOMPE'FARMACEUTICI SPA) 15 September 1994 ENTIRE DOCUMENT. --- | 1-9 |
| A | US,A,5 179 097 (ANGRES) 12 January 1993 see claims 1,3,8 ----- | 1 |

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|---|---|---|---|
| WO-A-9420449 | 15-09-94 | AU-B- 6290594 | 26-09-94 |
| US-A-5179097 | 12-01-93 | NONE | |